REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-35 and 50-111 are pending. New claims 108-111 are added. Claims 1-29, 31-35, 50-61, 79-103 and 105-106 have been examined on the merits; nonelected claims 30, 62-78, 104 and 107 were withdrawn from consideration by the Examiner.

The amendments are supported by the original disclosure and, thus, no new matter has been added. If the Examiner should disagree, however, he is respectfully requested to point out the challenged limitation with particularity in the next Action so support may be cited in response. For example, new claims 108-111 are supported inter alia by page 15, lines 13-15, and page 17, lines 1-3, of the specification. Amended claims 28 and 90 are supported inter alia by page 5, lines 2-4, of the specification.

The Examiner is urged to reconsider his restriction requirement between Groups I and II. In the Office Action (Paper No. 28) mailed June 28, 2002, he stated that Group I was drawn to "a method of inducing an immune response comprising a formulation comprising an adjuvant and a pathogenic antigen to skin" and Group II was drawn to "a method of inducing an immune response comprising applying an adjuvant to skin." Applicants traversed the restriction requirement by noting that examination of Groups I and II would not constitute an undue burden as shown by the fact that both claims 1 and 30 were previously examined in this application. Furthermore, the pathogenic antigen and the adjuvant are not necessarily separate molecules of the formulation. In fact, an ADP-ribosylating exotoxin or a derivative thereof may have both antigen and adjuvant activities. The Examiner did not respond to either argument in the Office Action (Paper No. 30) mailed October 18, 2002. He stated that undue search burden had been established because "the methods comprise different reagents, or combinations thereof, administered in different ways" (page 2). But this overlooks the fact that those different reagents and ways of administration were examined in previous Office Actions. Thus, there is no undue burden here. Rejoinder of Groups I and II is requested.

The drawings were objected to by the Official Draftsperson. Formal drawings with appropriate corrections are submitted herewith.

35 U.S.C. 103 – Nonobviousness

Claim 3 was rejected under Section 103(a) as allegedly being unpatentable over (U.S. Patent 5,340,588 or Paul et al.) in view of Marinaro et al. and the "admitted prior art on page 16 of the specification." Applicants traverse.

Claim 3 was rejected under Section 103(a) as allegedly being unpatentable over U.S. Patent 5,340,588 in view of Paul et al. in view of Kosecka et al. the "admitted prior art on page 16 of the specification," and U.S. Patent 5,686,100. Applicants traverse.

The Examiner noted on page 2 of the Action (Paper No. 30) that Claim 3 recites a formulation which further comprises liposomes. He also acknowledges that claims 1 and 31-33 recite that an effective amount of the antigen is not encapsulated. But he alleges that the inclusion of liposomes in the formulation renders the method obvious in view of the prior art. Applicants disagree because to establish a case of prima facie obviousness, all claim limitations must be taught or suggested by the prior art (M.P.E.P. § 2143.03). Here, the cited references fail to teach or suggest that an effective amount of antigen is not encapsulated.

In contrast, Applicants teach on page 19, lines 17-18, of their specification that liposomes are not required to elicit an antigen-specific immune response. The recitation in claim 3 that there are liposomes in the formulation does not alter this reality because their presence does not require that they encapsulate all of the antigen. Even when liposomes are formed in the presence of antigen, some antigen may remain unencapsulated (see page 20, lines 9-19, of the specification). Alternatively, antigen may be mixed with pre-formed liposomes. In the latter situation, antigen would be in solution and/or associated with, but not encapsulated by, the liposomes (page 20, lines 23-26, of the specification). The liposomes recited in claim 3 may be used for hydration and/or to enhance penetration of the stratum corneum (page 20, lines 31-33, of the specification).

The Examiner's proposed combinations do not render obvious the claims under examination because the cited references do not teach or suggest all limitations of any one of independent claims 1 and 31-33. Therefore, claims depending from the independent claims are also not made obvious by the references because the limitations of

claim 1 or 31-33 are incorporated in the dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Withdrawal of the Section 103 rejection is requested because the invention would not have been obvious to a person of ordinary skill in the art at the time it was made.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 22-24 were rejected under Section 112, first paragraph, because the phrase "toxin or a derivative thereof" is allegedly not supported by the specification as originally filed (i.e., a new matter rejection). The Examiner asserted on page 5 of the Action (Paper No. 30) that the generic disclosure of "bAREs and a derivative thereof" is insufficient to support claims drawn to individual species. Support for derivatives of a specific bacterial ADP-ribosylating exotoxin (e.g., PT, CT, LT, DT, ETA) is found inter alia on pages 16-18 of the specification and were known in the prior art although not disclosed to be useful for transcutaneous immunization. Proteolytic or recombinantly-produced fragments of full-length bacterial ADP-ribosylating exotoxins, chemical or genetic modifications of wild-type bacterial ADP-ribosylating exotoxins, and chemical conjugates or recombinant fusions thereof would all be considered derivatives.

As taught by Applicants in their specification, the separate functions of A and B subunits and the ability to separate functions (e.g., ADP ribosylation, receptor binding) enables one to make the derivatives recited in the claims. Such derivatives were available as of the effective filing date of this application (i.e., November 14, 1996) and do not require further description in the specification. A specification need not teach, and preferably omits, what is well known in the art. See *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986). Thus, fragments (e.g., A or B subunits) do not need

to be specifically taught because making them by proteolysis or recombinant technology were known. Mutants of particular ADP-ribosylating exotoxins were also known as of the effective filing date of this application. Three examples of relevant publications are attached: Douce et al. (Proc. Natl. Acad. Sci. USA 92:1644-1648, 1995); Fontana et al. (Infect. Immun. 63:2356-2360, 1995); and Nashar et al. (Proc. Natl. Acad. Sci. USA 93:226-230, 1996). They describe "derivatives" within the scope of the claims which are useful in practice of transcutaneous immunization (n.b., these publications do not teach or suggest the claimed invention). In view of the teachings of Applicants' specification and what was known in the art, the challenged limitations are not new matter.

Claims 1-29, 31-35, 50-61, 79-103 and 105-106 were also rejected under Section 112, first paragraph, for alleged new matter as listed on pages 7-8 of the Action (Paper No. 30). Applicants traverse.

Support for antigen which is not encapsulated (claims 1 and 31-33) can be found on page 20, lines 23-26, of the specification. This negative limitation is also implicit in Examples 1-3 where it was shown that liposomes were not required in the formulation to induce an antigen-specific immune response.

Original claim 4 is incomplete but correction of this typographical error is clear from the discussion on page 3, lines 24-25, and page 5, lines 25-27, of the specification that the use of penetration enhancers is optional. Therefore, a physical, chemical, electrical, or sonic penentration enhancer may or may not be used in the claimed invention. This is made explicit in original claim 38.

Claim 15 has been restored to its original form.

Derivatives of bacterial ADP-ribosylating exotoxins (claims 25-26 and 85-90) are on pages 16-18 of the specification. Proteolytic or recombinantly-produced fragments of full-length bacterial ADP-ribosylating exotoxins, chemical or genetic modifications of wild-type bacterial ADP-ribosylating exotoxins, and chemical conjugates or recombinant fusions thereof would all be considered derivatives.

Genetically- or chemically-produced derivatives of an ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated (claim 51 or 52, respectively) are described on page 6, line 9, of the specification.

At least partial purification of the antigen or antigen molecule (claims 54-60 and 96-102) is described on page 17, lines 23-34, of the specification.

Claims 81 and 92 have been corrected to recite bacterial DNA, which adjuvant is described on page 18, line 32, of the specification.

Adjuvant binding to receptors on an antigen presenting cell (claims 82 and 93) is described on page 16, lines 26-33, of the specification.

Withdrawal of the written description rejection made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1-29, 31-35, 50-61, 79-103 and 105-106 were rejected under Section 112, first paragraph, because it was alleged that the specification does not reasonably provide enablement for the claims. Applicants traverse.

A mechanism by which the claimed invention may induce an antigen-specific immune response is taught on page 3, line 35, to page 4, line 6, of the specification. This proposed mechanism is discussed in further detail on page 47, line 11, to page 49, line 19, of the specification. Example 17 is a direct demonstration that the application of adjuvant causes activation of antigen presenting cells (e.g., Langerhans cells).

The Examiner asserts on page 7 of the Action (Paper No. 30) that "claims reciting specific aspects of a mechanism by which the claimed method might function would require some specific demonstration of enablement." *In re Wands* is discussed in the next paragraph, but it does not appear that this case has been cited in support of

the Examiner's assertion. In fact, no authority is cited. Applicants submit that their teaching should be accepted as objectively true in the absence of any evidence or reasoning which is inconsistent with the proposed mechanism. See *In re Marzocchi*.

If this rejection is maintained, the Examiner is respectfully requested to cite authority for his assertion or, in the absence of legal authority contradicting *Marzocchi*, to make "acceptable evidence or reasoning" of record which is inconsistent with claims 1 and 32-33. As stated in M.P.E.P. § 2164.04, "[S]pecific technical reasons are always required" to support a prima facie case of lack of enablement. Because such evidence would constitute a new grounds for rejection, Applicant also request the opportunity to respond prior to a final rejection.

Finally, the Examiner did find that the specification was enabling for "a method of inducing an immune response comprising hydrating intact skin and applying a formulation to intact skin of an organism, wherein the formulation comprises at least one ADP-ribosylating exotoxin adjuvant and an effective amount of an antigen derived from a pathogen." Applicants submit that at least independent claims 30-31 and 62 as well as claims depending therefrom are enabled in accordance with the Examiner's finding.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 112 – Definiteness

Claims 20-21 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse because the phrase "ADP-ribosylating exotoxin" has been deleted from claims 20-21.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

Conclusion

Having fully responded to all of the pending objections and rejections contained in the Office Action (Paper No. 30), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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APPENDIX
MARKED-UP VERSION TO SHOW CHANGES

IN THE CLAIMS

The claims are amended as follows.

1. (4x Amended) A method of inducing an immune response comprising:

(a) hydrating intact skin of an organism and applying a formulation to the hydrated, intact skin [of an organism], wherein the formulation comprises (i) at least one antigen which is derived from a pathogen and (ii) at least one adjuvant, and an effective amount of the antigen which is not encapsulated induces the immune response;

(b) activating a Langerhans cell with the at least one adjuvant; and

(c) presenting the at least one antigen or epitope thereof on a cell surface of the Langerhans cell to a lymphocyte, thereby inducing the immune response in the organism.

3. (Amended) The method of claim 31, wherein the formulation further comprises liposomes.

4. (3x Amended) The method of claim 31, wherein a physical, chemical, electrical, or sonic penetration enhancer is not used.

5. (Amended) The method of claim 31, wherein the immune response is not an allergic reaction.

6. (Amended) The method of claim 31 further comprising applying alcohol to the intact skin prior to application of the formulation.

10. (Amended) The method of claim 31, wherein the antigen has a molecular weight greater than 500 daltons.

11. (2x Amended) The method of claim 31, wherein the antigen is derived from a bacterium.

12. (2x Amended) The method of claim 31, wherein the antigen is derived from a virus.

13. (2x Amended) The method of claim 31, wherein the antigen is derived from a fungus or parasite.

14. (Amended) The method of claim 31, wherein the antigen is selected from the group consisting of carbohydrate, glycolipid, glycoprotein, lipid, lipoprotein, phospholipid, and polypeptide.

15. (2x Amended) The method of claim 31, wherein the formulation comprises a live or an attenuated live virus [or virosome;] and the antigen is expressed by the live or attenuated live virus [or virosome, which is not encapsulated].

16. (Amended) The method of claim 31, wherein the antigen is a polypeptide of greater than 500 daltons molecular weight.

17. (Amended) The method of claim 31, wherein the antigen is multivalent.

20. (2x Amended) The method of claim 1, wherein said at least one adjuvant [the ADP-ribosylating exotoxin] activates the Langerhans cell.

21. (2x Amended) The method of claim 1, wherein said at least one adjuvant [the ADP-ribosylating exotoxin] enhances antigen presentation to a lymphocyte.

27. (2x Amended) The method of claim 31, wherein the formulation is a cream or gel or emulsion or ointment.

28. (Amended) The method of claim 1, wherein the formulation further comprises a [is applied with an occlusive] dressing.

29. (Amended) The method of claim 31, wherein the formulation is applied to intact skin covering more than one draining lymph node field.

30. (3x Amended) A method of immunization comprising hydrating intact skin of an organism and applying a formulation to the hydrated, intact skin [of an organism], wherein the formulation consists essentially of one or more ADP-ribosylating exotoxins or derivatives thereof having adjuvant activity, and an effective amount of said one or more ADP-ribosylating exotoxins or derivatives thereof is not encapsulated.

31. (3x Amended) A method of inducing an immune response comprising:
(a) hydrating intact skin of an organism and applying a formulation to the hydrated, intact skin [of an organism], wherein the formulation comprises (i) at least one antigen which is derived from a pathogen and (ii) at least one adjuvant comprising an ADP-ribosylating exotoxin or derivative thereof, and at least some antigen which is not encapsulated induces the immune response; and
(b) inducing the immune response in the organism without perforating the skin, wherein the immune response is specific for the antigen.

32. (4x Amended) A method of inducing an immune response comprising:
(a) hydrating intact skin of an organism and applying a formulation to the hydrated, intact skin [of an organism], wherein the formulation comprises (i) at least one antigen which is derived from a pathogen and (ii) at least one adjuvant comprising an ADP-ribosylating exotoxin or derivative thereof, and at least some antigen which is not encapsulated induces the immune response;
(b) activating an antigen presenting cell with the at least one adjuvant; and

(c) presenting the at least one antigen or epitope thereof on a cell surface of the antigen presenting cell to a lymphocyte, thereby inducing the immune response in the organism.

33. (3x Amended) A method of inducing an immune response comprising:
(a) applying epicutaneously to hydrated, intact skin of [on] an organism an effective amount of at least one antigen derived from a pathogen and which is not encapsulated,
(b) activating a Langerhans cell underlying the organism's skin with at least one adjuvant comprising an ADP-ribosylating exotoxin or derivative thereof,
(c) signaling the Langerhans cell to migrate to a lymph node of the organism and mature into a dendritic cell therein, and
(d) presenting the at least one antigen or epitope thereof on a cell surface of the dendritic cell to a lymphocyte; thereby inducing the immune response in the organism, wherein the immune response is specific for the at least one antigen.

61. (Amended) The method of claim 31, wherein the formulation comprises a whole organism, and the antigen is expressed by the whole organism [which is not encapsulated].

62. (2x Amended) A method of immunization comprising hydrating intact skin of an organism and applying a formulation without lipid vesicles to the hydrated, intact skin [of an organism], wherein the formulation is comprised of an effective amount of one or more at least partially purified ADP-ribosylating exotoxins or derivatives thereof having adjuvant activity.

81. (Amended) The method of claim 1, wherein at least one adjuvant is bacterial DNA [from bacteria or containing unmethylated CpG motifs].

82. (Amended) The method of claim 1, wherein at least one adjuvant is an ADP-ribosylating exotoxin or a derivative thereof which binds a receptor on antigen presenting cells.

90. (Amended) The method of claim 31, wherein the formulation further comprises a dressing [at least one adjuvant is an ADP-ribosylating exotoxin or derivative thereof having adjuvant activity].

91. (Amended) The method of claim 31, wherein at least one adjuvant is further comprised of a cytokine or a chemokine.

92. (Amended) The method of claim 31, wherein at least one adjuvant is further comprised of bacterial DNA [from bacteria or containing unmethylated CpG motifs].

93. (Amended) The method of claim 31, wherein at least one adjuvant is an ADP-ribosylating exotoxin or a derivative thereof which binds a receptor on antigen presenting cells.

103. (Amended) The method of claim 1 further comprising [hydrating the intact skin and] applying the formulation with an occlusive dressing.

104. (Amended) The method of claim 30 further comprising [hydrating the intact skin before application of the formulation and] applying the formulation with an occlusive dressing.

105. (Amended) The method of claim 31 further comprising [hydrating the intact skin before application of the formulation and] applying the formulation with an occlusive dressing.

106. (Amended) The method of claim 32 further comprising [hydrating the intact skin before application of the formulation and] applying the formulation with an occlusive dressing.

107. (Amended) The method of claim 62 further comprising [hydrating the intact skin before application of the formulation and] applying the formulation with an occlusive dressing.

Claims 108-111 are added.